REMARKS

Support for amended claim 1 can be found in the specification, for example, on page 2, lines 1-2. Support for new claims 9-24 can be found throughout the specification, for example, on page 14, lines 10-16, and in the originally filed claims.

Rejection of Claims 1-8 Under 35 U.S.C. §112, ¶ 2 – Indefiniteness

The Examiner has rejected claims 1-8 under 35 U.S.C. §112, ¶ 2 for indefiniteness. The Examiner contends that the phrase "basement membrane tissue" in claim 1 is indefinite because basement membrane is acellular and a tissue is an aggregate of cells, according to the Examiner. Additionally, the Examiner contends that claims 1-8 are indefinite because, according to the Examiner, the specification describes the use of basement membranes that are devoid of endogenous cellular components, but the claims do not require that the graft constructs be devoid of endogenous cellular components.

Claim 1 has been amended to replace the phrase "basement membrane tissue" with "basement membrane," and to specify that the liver basement membrane is "substantially free of endogenous cells." Thus, claim 1 has been amended in line with the Examiner's suggestions and claim 1 is definite.

Finally, the Examiner has rejected claim 8 as being of improper dependent form for failing to limit the subject matter of claim 6. Respectfully, the Examiner has failed to appreciate the distinction between a multilayered "homolaminate" graft composition and a multilayered graft composition formed from two or more layers. The specification, on page 13, line 22, describes a "homolaminate" graft composition as a graft composition having the *same number of layers throughout the graft*. Therefore, the term "homolaminate" further

limits the subject matter of claim 6, and claim 8 is properly dependent from claim 6. Withdrawal of the rejection of claims 1-8 under 35 U.S.C. § 112, ¶ 2, for all of the reasons discussed above, is respectfully requested.

Rejection of Claims 1-5 Under 35 U.S.C. §112, ¶ 1 – Written Description

The Examiner has rejected claims 1-5, stating that the application as filed fails to show that Applicants had possession of an invention as broad as claimed in claim 1, which refers to the use of "basement membranes" generally. The Examiner contends that the claims cover the use of basement membranes from all tissue types, but the specification provides written description support only for the use of "liver basement membranes" to repair liver tissue.

Claim 1 has been amended to replace the phrase "basement membrane" with "liver basement membrane" as suggested by the Examiner. Accordingly, the Examiner's rejection is overcome. Applicants respectfully request withdrawal of the rejection of claims 1-5 under 35 U.S.C. § 112, ¶ 1.

Rejection of Claims 1-8 Under 35 U.S.C. §112, ¶ 1 – Enablement

The Examiner has rejected claims 1-8 for lack of enablement. The Examiner contends that the application does not enable the use of "basement membranes" generally, but, rather, the use of "liver basement membranes" to repair liver tissue. The Examiner also contends that the specification enables the use of liver basement membranes that are devoid of cells endogenous to the liver tissue, but not liver basement membrane "tissue" which, as interpreted by the Examiner, comprises cells.

In line with the Examiner's suggestions, claim 1 has been amended to specify the use of "liver basement membranes" that are "substantially free of endogenous cells". Accordingly, the Examiner's rejection for lack of enablement has been overcome. Withdrawal of the rejection of claims 1-8 under 35 U.S.C. § 112, ¶ 1 is respectfully requested.

Rejection of Claims 1-8 Under 35 U.S.C. §103(a) and for Obviousness-Type Double-Patenting

The Examiner has rejected claims 1-8 under 35 U.S.C. §103 as being obvious over WO 98/25637 (the '637 application) and U.S. Patent No. 6,793,939 (the '939 patent). The Examiner contends that one would have reasonable anticipation of success in repairing liver tissue based on the disclosure in these documents. In particular, the Examiner cites a statement in column 8, lines 55-65 of the '939 patent that liver basement membranes can be used to stimulate proliferation of hepatocytes. In addition, under the doctrine of obviousness-type double-patenting, the Examiner contends that claims 1-8 are unpatentable over claims 1-14 of the '939 patent. The Examiner contends that the only difference between claims 1-14 of the '939 patent and claims 1-8 of the present application is that the '939 patent claims are generic to the repair of any tissue type, whereas the claims of the present application are specific to the repair of liver tissue.

Although Applicants disagree that the Examiner has established a *prima facie* case of obviousness sufficient to support the Examiner's rejections under 35 U.S.C. §103 and for obviousness-type double-patenting, the Examiner's rejections under 35 U.S.C. § 103(a) and for obviousness-type double-patenting are overcome by unexpected results obtained by Applicants. Applicants have shown that *functional* hepatocytes can be maintained in culture using liver basement membrane as a substrate. As the court concluded in *In re Diamond*, the question of nonobviousness must turn on whether the *prima facie* case of obviousness of the

claimed composition is rebutted by a showing of unexpected results. *In re Diamond*, 53 CCPA 1172, 360 F.2d 214, 149 USPQ 562 (1966). *In re Meinhardt*, 55 CCPA 1000, 392 F.2d 273, 157 USPQ 270 (1968).

As indicated by the Examiner, the '637 application and the '939 patent mention that liver basement membranes might be useful to *stimulate proliferation* of undifferentiated or differentiated cells (column 8, lines 55-59 and page 12, lines 3-6, respectively). Each reference also lists examples of differentiated cells, including hepatocytes. However, even if one skilled in the art expected to stimulate the *proliferation* of hepatocytes (*i.e.*, increase their number) by using liver basement membrane compositions as a substrate, there is no expectation that liver basement membranes could be used for *maintenance of hepatocyte functionality*.

Mere hepatocyte proliferation in culture does not translate into maintenance of hepatocyte functionality. The great degree of difficulty in maintaining the functionality of hepatocytes in culture is well-known to those skilled in the art. Therefore, one skilled in the art would not expect to maintain *functional* hepatocytes using liver basement membrane as a substrate. Numerous publications provide evidence that those skilled in the art would not expect that hepatocytes cultured on liver basement membrane would maintain hepatocellular function, as was surprisingly found by Applicants. For example, see Yamamoto et al., *Hepatology Research* 35(3):169-77 (2006) (abstract), stating that "Long-term culture of primary hepatocytes from various species is impeded by a decrease in cell viability and a *loss of hepatocytes-specific function.*" (emphasis added); Wang YJ et al., *World J. Gastroenterol.* 10(5):699-702 (2004) stating that "[I]t is *difficult to maintain the physiological function of hepatocytes*, leading to restriction of their extensive uses." (emphasis added); and Campbell LH et al., *In Vitro Cell Dev. Bio. Meeting,* 2007, (abstract A-2000) stating "[Hepatocyte]

specific functions are lost in culture relatively quickly." (emphasis added). These references are included as references 1-3 in an Information Disclosure Statement submitted with this response.

Specifically, hepatocyte culture on liver basement membrane was found by Applicants to be unexpectedly superior to conventional hepatocyte culture on adsorbed collagen and hepatocytes were found to maintain synthetic and metabolic functions when cultured on liver basement membranes. For example, albumin production, a measure of liver synthetic function, was found to be maintained or elevated in hepatocytes cultured on liver basement membrane, whereas albumin production declined in hepatocytes cultured on adsorbed collagen. (See page 22, lines 19-21 in the instant application). The synthetic and metabolic functions were not only superior to culture on adsorbed collagen, but were also comparable to culture on a double-gel collagen substrate, a substrate with known capacity for maintaining hepatocyte synthetic and metabolic functions. (See page 22, lines 16-18 in the instant application).

Also, urea content, a measure of liver metabolic function, was found to be about the same in hepatocytes cultured on liver basement membrane, on a per cell basis, as that from cells grown on a double-gel substrate. (See page 22, line 32 to page 23, line 1 in the instant application). Additionally, in hepatocytes cultured on liver basement membrane, cytochrome P450 activity, a measure of liver metabolic activity, was at least as high if not greater than that for hepatocytes grown on a double-gel substrate. (See page 23, lines 27-31 in the instant application). These results together show that hepatocytes grown on liver basement membranes exhibit specific liver synthetic and metabolic activity characteristic of *functional hepatocytes*, results that are unexpected based on the well-known difficulties associated with maintaining hepatocellular-specific functions in cultured hepatocytes.

Accordingly, even if the Examiner has established a *prima facie* case of obviousness, and Applicants contend that the Examiner has not, Applicants have overcome the Examiner's *prima facie* case of obviousness by demonstrating that Applicants' claimed methods and compositions unexpectedly result in a level of hepatocyte functionality that is difficult to obtain. Withdrawal of the rejections of claims 1-8 under 35 U.S.C. § 103(a) and for obviousness-type double-patenting is respectfully requested.

CONCLUSION

The claims are believed to be allowable. Passage of the application to issuance is requested.

Respectfully submitted,

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